

Claims

1. A method for screening, diagnosis or prognosis of Cardiac Response in a subject, for determining the stage or severity of Cardiac Response in a subject, for identifying a subject at risk of developing Cardiac Response, or for monitoring the effect of therapy administered to a subject having Cardiac Response, said method comprising:

(a) analyzing a test sample of a body fluid or tissue from the subject by two dimensional electrophoresis to generate a two-dimensional array of features, said array comprising at least one chosen feature whose relative abundance correlates with the presence, absence, stage or severity of Cardiac Response or predicts the onset or course of Cardiac Response; and

(b) comparing the abundance of each chosen feature in the test sample with the abundance of that chosen feature in body fluid from one or more subjects free from Cardiac Response, or with a previously determined reference range for that feature in subjects free from Cardiac Response, or with the abundance at least one Expression Reference Feature (ERF) in the test sample.

2. The method of claim 1, wherein the body fluid is blood.

3. The method of claim 1 or claim 2, wherein said method is for screening or diagnosis of Cardiac Response and the relative abundance of at least one chosen feature correlates with the presence or absence of Cardiac Response.

4. The method of claim 1 or claim 2, wherein said method is for monitoring the effect of therapy administered to a subject having Cardiac Response and the relative abundance of at least one chosen feature correlates with the severity of Cardiac Response.

5. The method of claim 2, wherein step (b) comprises comparing the abundance of each chosen feature in the sample with the abundance of that chosen feature in blood from one or more persons free from Cardiac Response or with a

previously determined reference range for that chosen feature in subjects free from Cardiac Response.

6. The method according to claim 1, 2, or 5, wherein step (b) comprises quantitatively detecting one or more of the following Cardiac Response-Associated Features (CRFs): CRF-1, CRF-2, CRF-3, CRF-4, CRF-5, CRF-6, CRF-7, CRF-8, CRF-9, CRF-10, CRF-11, CRF-12, CRF-13, CRF-14, CRF-15, CRF-17, CRF-18, CRF-19, CRF-20, CRF-21, CRF-22, CRF-28, CRF-42, CRF-43, CRF-44, CRF-45, CRF-47, CRF-49, CRF-51, CRF-52, CRF-53, CRF-54, CRF-56, CRF-58, CRF-59, CRF-62, CRF-66, CRF-69, CRF-72, CRF-73, CRF-79, CRF-80, CRF-82, CRF-83, CRF-84, CRF-87, CRF-89, CRF-90, CRF-92, CRF-94, CRF-95, CRF-96, CRF-98, CRF-99, CRF-100, CRF-102, CRF-103, CRF-104, CRF-105, CRF-112, CRF-113, CRF-115, CRF-116, CRF-118, CRF-119, CRF-120, CRF-121, CRF-122, CRF-124, CRF-127, CRF-128, CRF-129, CRF-130, CRF-131, CRF-132, CRF-134, CRF-135, CRF-136, CRF-140, CRF-141, CRF-142, CRF-143, CRF-144, CRF-145, CRF-146, CRF-147, CRF-148, CRF-149, CRF-150, CRF-151, CRF-152, CRF-153, CRF-154, CRF-155, CRF-156, CRF-157, CRF-158, CRF-159, CRF-160, CRF-161, CRF-162, CRF-163, CRF-164, CRF-165, CRF-166, CRF-167, CRF-168, CRF-169, CRF-170, CRF-171, CRF-172, CRF-173, CRF-174, CRF-175, CRF-176, CRF-177, CRF-178, CRF-179, CRF-180, CRF-181, CRF-182, CRF-183, CRF-184, CRF-185, CRF-186, CRF-187, CRF-188, CRF-189, CRF-190.

7. The method according to claim 1, 2, or 5, wherein step (a) comprises isoelectric focussing followed by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE).

8. A method for screening, diagnosis or prognosis of Cardiac Response in a subject, for determining the stage or severity of Cardiac Response in a subject, for identifying a subject at risk of developing Cardiac Response, or for monitoring the effect of therapy administered to a subject having Cardiac Response, said method comprising quantitatively detecting, in a sample of serum from the subject, at least one of the following Cardiac Response-Associated Protein Isoforms (CRPIs): CRPI-

1, CRPI-2, CRPI-4, CRPI-5, CRPI-7, CRPI-8, CRPI-10, CRPI-11, CRPI-14, CRPI-15, CRPI-19, CRPI-43, CRPI-44, CRPI-51, CRPI-52, CRPI-54, CRPI-56, CRPI-59, CRPI-69, CRPI-92.1, CRPI-92.2, CRPI-95, CRPI-100, CRPI-105, CRPI-122, CRPI-124, CRPI-132, CRPI-134, CRPI-140, CRPI-150, CRPI-154, CRPI-156, CRPI-164,

9. The method according to claim 8, wherein the step of quantitatively detecting comprises testing at least one aliquot of the sample, said step of testing comprising:

- (a) contacting the aliquot with an antibody that is immunospecific for a preselected CRPI; and
- (b) quantitatively measuring any binding that has occurred between the antibody and at least one species in the aliquot.

10. The method according to claim 9, wherein the antibody is a monoclonal antibody.

11. The method according to claim 9, wherein the step of quantitatively detecting comprises testing a plurality of aliquots with a plurality of antibodies for quantitative detection of a plurality of preselected CRPIs.

12. The method according to claim 11, wherein the antibodies are monoclonal antibodies.

13. A preparation comprising one or more of the following isolated or recombinant Cardiac Response-Associated Protein Isoforms (CRPIs): CRPI-1, CRPI-2, CRPI-4, CRPI-5, CRPI-7, CRPI-8, CRPI-10, CRPI-11, CRPI-14, CRPI-15, CRPI-19, CRPI-43, CRPI-44, CRPI-51, CRPI-52, CRPI-54, CRPI-56, CRPI-59, CRPI-69, CRPI-92.1, CRPI-92.2, CRPI-95, CRPI-100, CRPI-105, CRPI-122, CRPI-124, CRPI-132, CRPI-134, CRPI-140, CRPI-150, CRPI-154, CRPI-156, CRPI-164.

14. A preparation of claim 13, wherein the PCPI is in a recombinant form.

16. A kit comprising the preparation of claims 14 or 15.

17. A kit comprising a plurality preparations of claim 13.

18. An antibody capable of immunospecific binding to one of the following Cardiac Response-Associated Protein Isoforms (CRPIs): CRPI-1, CRPI-2, CRPI-4, CRPI-5, CRPI-7, CRPI-8, CRPI-10, CRPI-11, CRPI-14, CRPI-15, CRPI-19, CRPI-43, CRPI-44, CRPI-51, CRPI-52, CRPI-54, CRPI-56, CRPI-59, CRPI-69, CRPI-92.1, CRPI-92.2, CRPI-95, CRPI-100, CRPI-105, CRPI-122, CRPI-124, CRPI-132, CRPI-134, CRPI-140, CRPI-150, CRPI-154, CRPI-156, CRPI-164,

19. The antibody of claim 18, which is a monoclonal antibody.

19. The antibody of claim 18 or 19, which binds to the CRPI with greater affinity than to another isoform of the CRPI.

20. The antibody of claim 18, which binds to the CRPI with greater affinity than to any other isoform of the CRPI.

21. A kit comprising the antibody of claim 18.

22. A kit comprising a plurality of distinct antibodies of claim 18.

23. A pharmaceutical composition comprising a therapeutically effective amount of an antibody of claim 18 and a pharmaceutically acceptable carrier.

24. A pharmaceutical composition comprising:

(a) a therapeutically effective amount of a fragment or derivative of an antibody of claim 18, said fragment or derivative containing the binding domain of the antibody; and

(b) a pharmaceutically acceptable carrier.

25. A method of treating or preventing Cardiac Response comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of a nucleic acid encoding one of the following Cardiac Response-Associated Protein Isoforms (CRPIs): CRPI-1, CRPI-2, CRPI-4, CRPI-5, CRPI-7, CRPI-8, CRPI-10, CRPI-11, CRPI-14, CRPI-15, CRPI-19, CRPI-43, CRPI-44, CRPI-51, CRPI-52, CRPI-54, CRPI-56, CRPI-59, CRPI-69, CRPI-92.1, CRPI-92.2, CRPI-95, CRPI-100, CRPI-105, CRPI-122, CRPI-124, CRPI-132, CRPI-134, CRPI-140, CRPI-150, CRPI-154, CRPI-156, CRPI-164, or an ortholog thereof.

26. A method of treating or preventing Cardiac Response comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of a nucleic acid that inhibits the function of one or more of the following Cardiac Response-Associated Protein Isoforms (CRPIs): CRPI-1, CRPI-2, CRPI-4, CRPI-5, CRPI-7, CRPI-8, CRPI-10, CRPI-11, CRPI-14, CRPI-15, CRPI-19, CRPI-43, CRPI-44, CRPI-51, CRPI-52, CRPI-54, CRPI-56, CRPI-59, CRPI-69, CRPI-92.1, CRPI-92.2, CRPI-95, CRPI-100, CRPI-105, CRPI-122, CRPI-124, CRPI-132, CRPI-134, CRPI-140, CRPI-150, CRPI-154, CRPI-156, CRPI-164, or an ortholog thereof.

27. The method of claim 26, wherein the nucleic acid is a CRPI antisense nucleic acid or ribozyme.

28. A method of screening for agents that interact with a CRPI, a CRPI fragment, or a CRPI-related polypeptide, said method comprising:

- (a) contacting a CRPI, a CRPI fragment, or a CRPI-related polypeptide with a candidate agent; and
- (b) determining whether or not the candidate agent interacts with the CRPI, the CRPI fragment, or the CRPI-related polypeptide.

29. The method of claim 28, wherein the CRPI, the CRPI fragment, or the CRPI-related polypeptide is expressed by cells.

30. The method of claim 29, wherein the cells express a recombinant CRPI, a recombinant CRPI fragment, or a recombinant CRPI-related polypeptide.

31. A method of screening for agents that modulate the expression or activity of a CRPI, a CRPI fragment or a CRPI-related polypeptide comprising:

- (a) contacting a first population of cells expressing a CRPI, a CRPI fragment or a CRPI-related polypeptide with a candidate agent;
- (b) contacting a second population of cells expressing said CRPI, said CRPI fragment or said CRPI-related polypeptide with a control agent; and
- (c) comparing the level of said CRPI, said CRPI fragment or said CRPI-related polypeptide or mRNA encoding said CRPI, said CRPI fragment or said CRPI-related polypeptide in the first and second populations of cells, or comparing the level of induction of a cellular second messenger in the first and second populations of cells.

32. The method of claim 31, wherein the level of said CRPI, said CRPI fragment or said CRPI-related polypeptide, mRNA encoding said CRPI, said CRPI fragment or said CRPI-related polypeptide, or said cellular second messenger is greater in the first population of cells than in the second population of cells.

33. The method of claim 31, wherein the level of said CRPI, said CRPI fragment or said CRPI-related polypeptide, mRNA encoding said CRPI, said CRPI fragment or said CRPI-related polypeptide, or said cellular second messenger is less in the first population of cells than in the second population of cells.

34. A method of screening for or identifying agents that modulate the expression or activity of a CRPI, a CRPI fragment or a CRPI-related polypeptide comprising:

- (a) administering a candidate agent to a first mammal or group of mammals;
- (b) administering a control agent to a second mammal or group of mammals; and

(c) comparing the level of expression of the CRPI, the CRPI fragment or the CRPI-related polypeptide or of mRNA encoding the CRPI, the CRPI fragment or the CRPI-related polypeptide in the first and second groups, or comparing the level of induction of a cellular second messenger in the first and second groups.

35. The method of claim 34, wherein the mammals are animal models for Cardiac Response.

36. The method of claim 34 or 35, wherein the level of expression of said CRPI, said CRPI fragment or said CRPI-related polypeptide, mRNA encoding said CRPI, said CRPI fragment or said CRPI-related polypeptide, or of said cellular second messenger is greater in the first group than in the second group.

37. The method of claim 34 or 35, wherein the level of expression of said CRPI, said CRPI fragment or said CRPI-related polypeptide, mRNA encoding said CRPI, said CRPI fragment or said CRPI-related polypeptide, or of said cellular second messenger is less than in the first group than in the second group.

38. The method of claim 34, wherein the levels of said CRPI, said CRPI fragment or said CRPI-related polypeptide, mRNA encoding said CRPI, said CRPI fragment or said CRPI-related polypeptide, or of said cellular second messenger in the first and second groups are further compared to the level of said CRPI, said CRPI fragment or said CRPI-related polypeptide or said mRNA encoding said CRPI, said CRPI fragment or said CRPI-related polypeptide in normal control mammals.

39. The method of claim 34, wherein administration of said candidate agent modulates the level of said CRPI, said CRPI fragment or said CRPI-related polypeptide, or said mRNA encoding said CRPI, said CRPI fragment or said CRPI-related polypeptide, or said cellular second messenger in the first group towards the levels of said CRPI, said CRPI fragment or said CRPI-related polypeptide or said mRNA or said cellular second messenger in the second group.

40. The method of claim 34, wherein said mammals are human subjects having Cardiac Response.

41. A method of screening for or identifying agents that interact with a CRPI, a CRPI fragment or a CRPI-related polypeptide, comprising

(a) contacting a candidate agent with the CRPI, the CRPI fragment or the CRPI-related polypeptide, and

(b) quantitatively detecting binding, if any, between the agent and the CRPI, the CRPI fragment or the CRPI-related polypeptide.

42. A method of screening for or identifying agents that modulate the activity of a CRPI, said CRPI fragment or a CRPI-related polypeptide, comprising

(a) in a first aliquot, contacting a candidate agent with the CRPI, said CRPI fragment or the CRPI-related polypeptide, and

(b) comparing the activity of the CRPI, said CRPI fragment or the CRPI-related polypeptide in the first aliquot after addition of the candidate agent with the activity of the CRPI, said CRPI fragment or the CRPI-related polypeptide in a control aliquot, or with a previously determined reference range.

43. The method according to claim 41 or 42, wherein the CRPI, the CRPI fragment or the CRPI-related polypeptide is recombinant protein.

44. The method according to claim 41 or 42, wherein the CRPI, the CRPI fragment or the CRPI-related polypeptide is immobilized on a solid phase.

45. A method for screening, diagnosis or prognosis of Cardiac Response in a subject or for monitoring the effect of an anti-Cardiac Response drug or therapy administered to a subject, comprising:

(a) contacting at least one oligonucleotide probe comprising 10 or more consecutive nucleotides complementary to a nucleotide sequence encoding a CRPI chosen from CRPI-1, CRPI-2, CRPI-4, CRPI-5, CRPI-7, CRPI-8, CRPI-10,

CRPI-11, CRPI-14, CRPI-15, CRPI-19, CRPI-43, CRPI-44, CRPI-51, CRPI-52, CRPI-54, CRPI-56, CRPI-59, CRPI-69, CRPI-92.1, CRPI-92.2, CRPI-95, CRPI-100, CRPI-105, CRPI-122, CRPI-124, CRPI-132, CRPI-134, CRPI-140, CRPI-150, CRPI-154, CRPI-156, CRPI-164, or an ortholog thereof, with an RNA obtained from a biological sample from the subject or with cDNA copied from the RNA wherein said contacting occurs under conditions that permit hybridization of the probe to the nucleotide sequence if present;

(b) detecting hybridization, if any, between the probe and the nucleotide sequence; and

(c) comparing the hybridization, if any, detected in step (b) with the hybridization detected in a control sample, or with a previously determined reference range.

46. The method of claim 45, wherein step (a) comprises contacting a plurality of oligonucleotide probes comprising 10 or more consecutive nucleotides complementary to a nucleotide sequence encoding a CRPI chosen from, CRPI-1, CRPI-2, CRPI-4, CRPI-5, CRPI-7, CRPI-8, CRPI-10, CRPI-11, CRPI-14, CRPI-15, CRPI-19, CRPI-43, CRPI-44, CRPI-51, CRPI-52, CRPI-54, CRPI-56, CRPI-59, CRPI-69, CRPI-92.1, CRPI-92.2, CRPI-95, CRPI-100, CRPI-105, CRPI-122, CRPI-124, CRPI-132, CRPI-134, CRPI-140, CRPI-150, CRPI-154, CRPI-156, CRPI-164, or an ortholog thereof, with an RNA obtained from a biological sample from the subject or with cDNA copied from the RNA wherein said contacting occurs under conditions that permit hybridization of the probe to the nucleotide sequence if present.

47. The method of claim 45, wherein step (a) includes the step of hybridising the nucleotide sequence to a DNA array, wherein one or more members of the array are the probes complementary to a plurality of nucleotide sequences encoding distinct CRPIs.

48. A method of modulating the activity of one or more of the following Cardiac Response-Associated Protein Isoforms (CRPIs): CRPI-1, CRPI-2, CRPI-4,

CRPI-5, CRPI-7, CRPI-8, CRPI-10, CRPI-11, CRPI-14, CRPI-15, CRPI-19, CRPI-43, CRPI-44, CRPI-51, CRPI-52, CRPI-54, CRPI-56, CRPI-59, CRPI-69, CRPI-92.1, CRPI-92.2, CRPI-95, CRPI-100, CRPI-105, CRPI-122, CRPI-124, CRPI-132, CRPI-134, CRPI-140, CRPI-150, CRPI-154, CRPI-156, CRPI-164, or an ortholog thereof, comprising the step of contacting a cell with an agent which specifically binds to one or more of the following Cardiac Response -Associated Protein Isoforms (CRPIs): CRPI-1, CRPI-2, CRPI-4, CRPI-5, CRPI-7, CRPI-8, CRPI-10, CRPI-11, CRPI-14, CRPI-15, CRPI-19, CRPI-43, CRPI-44, CRPI-51, CRPI-52, CRPI-54, CRPI-56, CRPI-59, CRPI-69, CRPI-92.1, CRPI-92.2, CRPI-95, CRPI-100, CRPI-105, CRPI-122, CRPI-124, CRPI-132, CRPI-134, CRPI-140, CRPI-150, CRPI-154, CRPI-156, CRPI-164, or an ortholog thereof, whereby the activity of the respective CRPI is modulated.

49. An agent that modulates the activity of one or more of the following Cardiac Response-Associated Protein Isoforms (CRPIs): CRPI-1, CRPI-2, CRPI-4, CRPI-5, CRPI-7, CRPI-8, CRPI-10, CRPI-11, CRPI-14, CRPI-15, CRPI-19, CRPI-43, CRPI-44, CRPI-51, CRPI-52, CRPI-54, CRPI-56, CRPI-59, CRPI-69, CRPI-92.1, CRPI-92.2, CRPI-95, CRPI-100, CRPI-105, CRPI-122, CRPI-124, CRPI-132, CRPI-134, CRPI-140, CRPI-150, CRPI-154, CRPI-156, CRPI-164, or an ortholog thereof, wherein said agent is identified by the method of any of claims 28, 31, 34, 41 or 42.

50. An agent as claimed in claim 49 for use in the manufacture of a medicament for the treatment or prevention of Cardiac Response.

51. A pharmaceutical composition, comprising:
the agent of claim 49 and a pharmaceutically acceptable carrier.

52. A method of treating or preventing cardiac response comprising administering to a subject in need of such treatment or prevention a therapeutically effective dose of an agent that modulates the activity of one or more of the following Cardiac Response-Associated Protein Isoforms (CRPIs): CRPI-1, CRPI-2, CRPI-4,

CRPI-5, CRPI-7, CRPI-8, CRPI-10, CRPI-11, CRPI-14, CRPI-15, CRPI-19, CRPI-43, CRPI-44, CRPI-51, CRPI-52, CRPI-54, CRPI-56, CRPI-59, CRPI-69, CRPI-92.1, CRPI-92.2, CRPI-95, CRPI-100, CRPI-105, CRPI-122, CRPI-124, CRPI-132, CRPI-134, CRPI-140, CRPI-150, CRPI-154, CRPI-156, CRPI-164, whereby the symptoms of cardiac response are ameliorated.

53. A method for identifying targets for therapeutic modulation of cardiac response wherein the activity of one or more of the following Cardiac Response-Associated Protein Isoforms (CRPIs): CRPI-1, CRPI-2, CRPI-4, CRPI-5, CRPI-7, CRPI-8, CRPI-10, CRPI-11, CRPI-14, CRPI-15, CRPI-19, CRPI-43, CRPI-44, CRPI-51, CRPI-52, CRPI-54, CRPI-56, CRPI-59, CRPI-69, CRPI-92.1, CRPI-92.2, CRPI-95, CRPI-100, CRPI-105, CRPI-122, CRPI-124, CRPI-132, CRPI-134, CRPI-140, CRPI-150, CRPI-154, CRPI-156, CRPI-164 is utilized as a measure to determine whether a candidate target is effective for modulation of cardiac response.